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EFFECTS OF BISOPROLOL AND ISOSORBIDE DINITRATE ON THE CIRCADIAN DISTRIBUTION OF MYOCARDIAL ISCHEMIA

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ABSTRACT

The effects of bisoprolol 10 mg once daily, isosorbide dinitrate (ISDN) 20 mg three times daily, or a combination of these drugs on ischemia during exercise testing and on the occurrence and the circadian variation of ischemia during ambulatory monitoring were evaluated in 23 patients with stable angina pectoris. ISDN and bisoprolol monotherapies both significantly reduced the number of patients with angina pectoris and ST-depression during ergometry while lengthening the time to occurrence of 0.1-mV ST-depression. ISDN did not reduce the number of ischemic episodes measured by Holter monitoring, although it did significantly reduce the duration of ischemia. Bisoprolol monotherapy and combination therapy significantly reduced the number of ischemic episodes as well as the duration of ischemia, total ischemic burden, and number of anginal attacks. The circadian variation of ischemia as measured by Holter monitor was completely abolished by bisoprolol monotherapy and by combination therapy. ISDN monotherapy reduced the evening peak of ischemia but only shortened the morning peak. Both bisoprolol and ISDN reduced ischemia during formal exercise testing, but only bisoprolol effectively reduced the total amount of daily life ischemia as measured by ambulatory monitoring.

INTRODUCTION

The problem of silent ischemia, defined as objective evidence for transient myocardial ischemia in the absence of symptoms, might be associated with adverse outcome,[1–3] although other evidence contradicts this.[4–6] Whether medical treatment of silent ischemia can influence prognosis is still under investigation.

Many episodes of silent ischemia occur during low levels of physical activity and during low heart rates, suggesting that not only an increased oxygen demand, but also changes in blood supply, might play a role. Cyclic variations of coronary vascular tone, heart rate, and blood pressure give

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rise to a clear circadian rhythm in the occurrence of ischemic episodes. The circadian distribution of transient myocardial ischemia usually shows a morning peak and a smaller secondary peak in the evening, while occurrences of myocardial infarction, ventricular tachycardia, sudden death, and cerebral stroke only show a morning peak.[7–9] It is conceivable that the different types of anti-ischemic drugs influence the circadian rhythm in different ways, according to their mechanisms of action. Likewise, the duration of action and the dosage schedule of an antianginal drug might influence its effect on the circadian variation of ischemia. So far, only beta-adrenergic blockers have proven to abolish the morning peak in the circadian variation of transient ischemia, myocardial infarction, and sudden death. Organic nitrates have proven their anti-ischemic efficacy, but few studies of the influence of nitrates on the circadian variation of ischemia have been performed.[10,11]

In this randomized, double-blind, placebo-controlled, crossover study, we investigated the effects of isosorbide dinitrate (ISDN) and bisoprolol on the occurrence and circadian distribution of silent and symptomatic ischemia during daily activities. ISDN is effective for approximately 2 to 8 hours after administration, and a nitrate-free interval is needed to avoid tolerance.[12–14] Bisoprolol is a highly $beta_1$-adrenergic–selective blocker with a long plasma-elimination half-life (10 to 12 hours), making it still effective 24 hours after administration. The combination of bisoprolol and ISDN was also studied to see whether this resulted in further beneficial effects.

We compared the number and duration of ischemic episodes during a 48-hour Holter registration, and the total exercise time, ST-depression, and anginal complaints during a bicycle exercise tolerance test (ETT) at the end of each treatment period.

PATIENTS AND METHODS

Patients

Patients aged 21 to 75 years with stable angina pectoris, angiographically proven coronary artery disease (at least one stenosis of $\geq$ 70%), at least 0.1-mV ST-depression during an ETT, and at least four ischemic episodes on a 48-hour Holter monitoring during the placebo phase were included. For women, coronary artery disease had to be proven by either a previous myocardial infarction, a positive exercise thallium scan, or a coronary angiogram. For men, coronary artery disease was proven by exercise test with $\geq$0.1-mV ST-depression.

Excluded from the study were women of childbearing age; patients with unstable angina, myocardial infarction <6 months prior to enrollment, severe angina, arrhythmias requiring medical treatment, severe

hypertension (diastolic >105 mm Hg), bradycardia (<45 beats/min), any degree of atrioventricular block, chronic obstructive pulmonary disease, hemodynamically important valvular disease, overt heart failure, and patients unable to exercise or with an uninterpretable ST-segment on electrocardiogram (ECG). Use of vasodilators, beta-adrenergic blockers, long-acting nitrates, and digitalis was forbidden during the study. The hospital ethics committee approved the protocol, and each patient gave written informed consent before entering the study.

Study Design

The study consisted of a 2-week single-blind placebo prephase and three randomized, double-blind, crossover treatment periods of 4 weeks each. There were no washout phases between the different treatments, but the 4-week treatment length ensured that the measurements at the end of each treatment could not be influenced by the previous treatment.

Treatment consisted of bisoprolol 10 mg once daily, or ISDN 20 mg three times daily (TID), or the combination, in random order. A double-dummy technique ensured the double blindness of the treatments.

Any current antianginal or vasodilator therapy was discontinued before the placebo phase. Only short-acting nitrates were allowed, but not prophylactically and not during the 2 hours immediately before the exercise tests. Patients were instructed to take their bisoprolol between 7 and 10 AM and the ISDN with every main meal. At each study visit investigators checked compliance. Patients kept a diary for recording complaints and adverse events, and they were questioned verbally at each visit.

On day 5, an ETT was performed 2 to 3 hours after medication intake. If at least 0.1 mV of horizontal or downsloping ST-depression occurred, a 48-hour Holter recording was obtained. A second ETT was performed on day 14; for inclusion in the study, patients had to have <15% variability in total exercise time. In addition, patients were required to have at least four episodes of silent ischemia on the 48-hour Holter recording. Patients fulfilling these criteria entered the active treatment phase of the study. Two days before the end of each treatment phase a 48-hour Holter registration was started. On the last day an ETT was performed 2 to 3 hours after medication intake.

The study ended with a final physical examination and a routine laboratory analysis (ie, erythrocyte sedimentation rate, hemoglobin, hematocrit, leukocyte count, sodium, potassium, urea, creatinine, lactic acid dehydrogenase, aspartate aminotransferase, alanine aminotransferase, and glucose) after the third active treatment period was completed.

Ambulatory ECG Analysis

The continuous 48-hour ambulatory ECG recordings were performed on 3-channel amplitude-modulated Marquette® recorders (Marquette

Electronics, Inc., Milwaukee, Wisconsin). We used modified leads aVF, V_1, and V_5. The computer analysis of each tape was manually checked by an experienced technician. Each episode of at least 0.1 mV of horizontal or downsloping ST-depression compared with baseline, measured 60 msec after the J-point, lasting for at least 1 minute, and separated from another episode by at least 1 minute of normalized ST-segment, was called ischemic.

The number and duration of ischemic episodes and the total ischemic burden, defined as the area under the curve, or duration of ST-depression multiplied by mm of ST-depression, were registered for each treatment period.

Exercise Tolerance Test

The supine bicycle exercise test started at a workload of 30 W. Every minute the workload increased by 10 W, until the patient stopped because of moderate angina, dyspnea, or fatigue. The ECG was monitored continuously, with a written conventional 12-lead ECG, blood pressure (BP), and heart rate (HR) registration at the end of each exercise level. Total exercise time, maximum workload, time to 0.1-mV ST-segment depression, maximum ST-depression, and time to angina were registered for each patient.

Statistical Analysis

Statistics were calculated using SPSS/PC+, version 4.01 (SPSS Inc., Chicago, Illinois). As the observed parameters were not normally distributed, Wilcoxon's matched-pairs signed-ranks test was used to compare treatment results with baseline values.

RESULTS

Patients

Of the 29 patients (27 men and 2 women) who entered the randomization phase, 6, all men, dropped out before the end of the study. One patient withdrew his consent, one had ventricular tachycardia, and four complained of severe headache. Of the patients who dropped out, 4 had previous myocardial infarction. The remaining 23 patients (21 men and 2 women) who completed the study were eligible for the efficacy analysis. Their mean age was 63 years (range, 41–76 y). Three patients had a previous myocardial infarction. Coronary angiography was performed in all patients: 19 patients had one-vessel disease, 2 had two-vessel disease, and 2 had three-vessel disease. Of the patients who dropped out, 1 had one-vessel disease, 3 had two-vessel disease, and 2 had three-vessel disease.

Exercise Test

After each active treatment fewer patients reached 0.1-mV ST-depression (Table I). The mean exercise time until the occurrence of 0.1-mV ST-depression increased 6% ($P < 0.05$) with ISDN, 17% with bisoprolol ($P = 0.05$), and 27% with the combination ($P = 0.05$).

The maximum ST-depression during exercise was 0.02 mV lower with ISDN ($P = 0.05$), 0.05 mV lower with bisoprolol ($P = 0.001$), and 0.07 mV lower with the combination ($P = 0.01$) than with placebo. Compared with ISDN monotherapy, bisoprolol monotherapy lowered maximum ST-depression 0.035 mV more ($P = 0.05$) and the combination 0.052 mV more ($P = 0.05$).

On active treatment significantly fewer patients had angina pectoris during the exercise test (Figure 1).

Ambulatory Monitoring

Although ISDN monotherapy did not significantly change the mean total number of ischemic episodes per 48 hours, the duration of the ischemic episodes was 55% shorter ($P = 0.05$) and the total ischemic burden 47% lower than with placebo ($P = 0.05$, Table II, Figure 2).

Bisoprolol monotherapy lowered the mean number of ischemic episodes per 48 hours by 74% ($P = 0.001$), the duration of ischemia by 82% ($P = 0.001$), and the total ischemic burden by 83% ($P = 0.001$) compared with placebo. Compared with ISDN monotherapy, the mean number of episodes was 69% lower with bisoprolol monotherapy ($P = 0.01$), the duration of

Table I. Comparison of exercise test data at the end of the placebo phase and at the end of each active treatment phase (n = 23). Values are expressed as mean ± SD except where noted.

	Placebo	ISDN	Bisoprolol	ISDN + Bisoprolol
Total exercise time (min:s)	9:01 ± 3:08	9:05 ± 3:04	9:11 ± 3:03	9:14 ± 2:49
Maximum workload (W)	113 ± 33	114 ± 29	115 ± 30	116 ± 28
Maximum heart rate (beats/min)	129 ± 22	127 ± 21	105 ± 20*	98 ± 27*
Maximum SBP (mm Hg)	187 ± 26	180 ± 33	165 ± 26*	164 ± 30*
Patients with ST-depression (n)	23	20	18	16
Time to 0.1-mV ST-depression (min:s)	5:52 ± 3:03	5:14 ± 2:34†	6:53 ± 2:27†	7:28 ± 3:02†
Maximum ST depression (mV)	0.20 ± 0.07	0.18 ± 0.07†	0.15 ± 0.06*‡	0.13 ± 0.06‡§
Patients with angina (n)	16	10†	10†	5*
Time to angina pectoris (min:s)	7:39 ± 2:57	7:56 ± 354	8:32 ± 3:08	8:51 ± 3:16

ISDN = isosorbide dinitrate; SBP = systolic blood pressure.
* $P < 0.01$ compared with placebo.
† $P < 0.05$ compared with placebo.
‡ $P < 0.05$ compared with ISDN alone.
§ $P < 0.001$ compared with placebo.

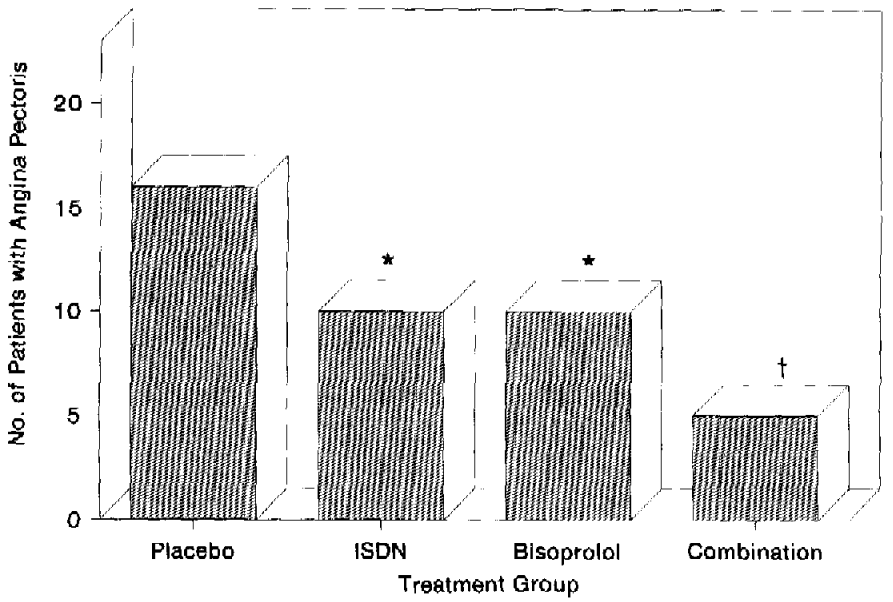

Figure 1. Number of patients with angina pectoris on exercise during each treatment phase. ISDN = isosorbide dinitrate. *$P < 0.05$, †$P < 0.01$ compared with placebo.

ischemia 61% shorter ($P = 0.05$), and the total ischemic burden 67% lower ($P = 0.05$).

The combination of bisoprolol and ISDN significantly lowered all Holter parameters compared with placebo as well as compared with ISDN alone. The combination was not significantly better than bisoprolol alone for any of the parameters. The combination decreased the mean number of

Table II. Comparison of mean Holter data per 48 hours during the placebo phase and at the end of each active treatment phase. Values are expressed as mean ± SD except where noted.

	Placebo	ISDN	Bisoprolol	ISDN + Bisoprolol
No. of ischemic episodes	9.8 ± 4.5	8.0 ± 8.8	2.5 ± 3.5*†	2.2 ± 3.3*†
Total duration of ischemia (min)	97 ± 101	44 ± 45‡	17 ± 33*§	12 ± 21*§
Total ischemic burden (mm × min)	186 ± 188	98 ± 129‡	32 ± 59*§	24 ± 47*§
No. of patients with angina	18	12	8	10
No. of anginal attacks/4 weeks	4.1 ± 3.0	4.0 ± 4.0	2.8 ± 2.0‖	2.6 ± 2.8‖
Percentage of silent ischemia (%)	92.0	98.2‡	99.5‡	99.5‡

ISDN = isosorbide dinitrate.
* $P < 0.001$ compared with placebo.
† $P < 0.01$ compared with ISDN alone.
‡ $P < 0.05$ compared with placebo.
§ $P < 0.05$ compared with ISDN alone.
‖ $P < 0.01$ compared with placebo.

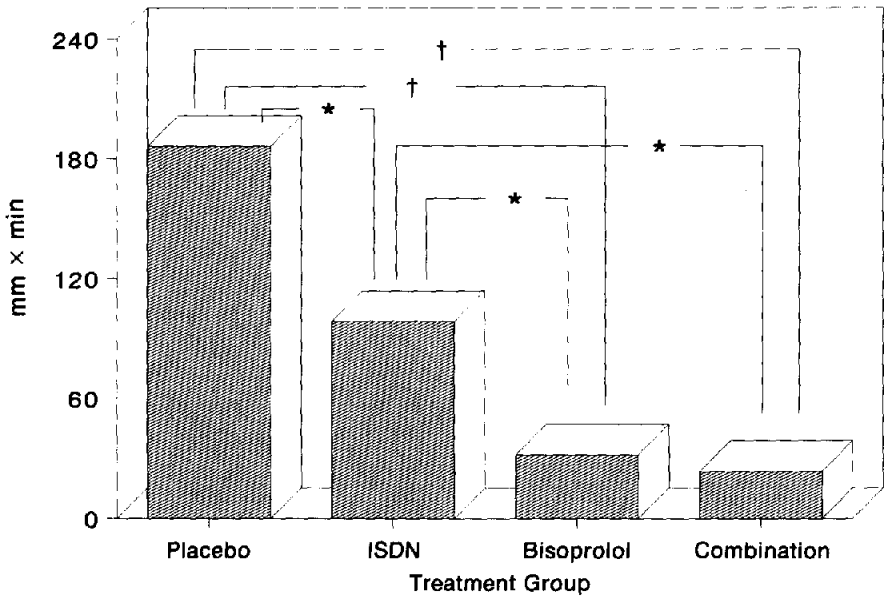

Figure 2. Mean total ischemic burden per 48 hours during different treatments. ISDN = isosorbide dinitrate. *$P < 0.05$, †$P < 0.001$.

ischemic episodes per 48 hours by 78% compared with placebo ($P = 0.001$), while the mean total duration of ischemia became 88% shorter ($P = 0.001$) and the mean total ischemic burden 87% lower ($P = 0.001$). Compared with ISDN alone the combination decreased the mean number of ischemic episodes by 73% ($P = 0.01$), the mean duration of ischemia by 73% ($P = 0.05$), and the total ischemic burden by 76% ($P = 0.05$).

Patients experienced significantly fewer anginal attacks when they were receiving treatment with bisoprolol alone or with the combination (Table II).

Circadian Variation of Ischemia

In the placebo phase, there was a clear circadian distribution of ischemic episodes, duration of ischemia, and total ischemic burden measured by 48-hour Holter monitoring (Figure 3), with a high morning peak and a lower late-afternoon/early-evening peak. Bisoprolol monotherapy as well as the combination of bisoprolol and ISDN completely abolished the morning and the evening peaks of ischemic events. ISDN treatment alone lowered the evening peak, although less than bisoprolol, and it only slightly narrowed the morning peak. When the day was divided into 6-hour periods, ISDN monotherapy significantly lowered the duration of ischemia

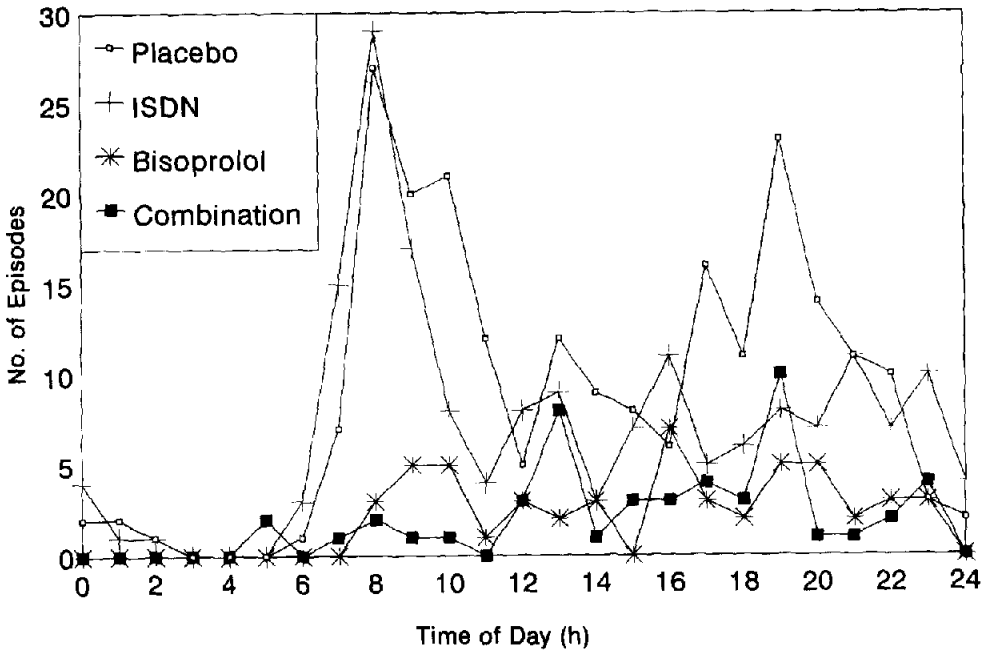

Figure 3. Circadian distribution of number of ischemic episodes per 24 hours during different treatments. ISDN = isosorbide dinitrate.

(P = 0.01) and the total ischemic burden (P = 0.01) between 6 and 12 PM.

Tolerance

Four patients dropped out of the study because of severe headache during ISDN treatment. One patient had ventricular tachycardia during the first active treatment phase with ISDN. Bisoprolol was generally well tolerated.

DISCUSSION

It is striking that the therapeutic differences between ISDN and bisoprolol were much more obvious during daily-activity Holter monitoring than during the exercise test. Whereas the Holter data showed large differences in the amount of silent ischemia in patients receiving ISDN or bisoprolol, both drugs were equally effective in reducing angina and ST-depression during ETT. Obviously, differences in anti-ischemic activity between drugs can be underestimated when only the ETT is used as a marker of efficacy. Also, in other studies similar discrepancies between ischemia during ETT or during daily activities have been shown. Studies with long-

acting nitrates showed that these drugs postpone the occurrence of anginal symptoms during exercise,[10] but so far only relatively little or no influence on ambulatory ischemia, and none at all on its circadian variation, have been shown.[10,15,16]

In our study, ISDN slightly altered the circadian variation of ischemia—the evening peak in duration of ischemia and in the total ischemic burden was significantly lowered, although less pronounced than with bisoprolol. Beta-adrenergic blockers such as atenolol, metoprolol, or propranolol effectively reduce both exercise-induced and ambulatory silent ischemia, abolishing the circadian variation,[15,17,18] and so does bisoprolol according to our study. Combination therapy with ISDN did not improve the effect of bisoprolol alone on the circadian variation of ischemia.

An explanation for the lack of effect of ISDN monotherapy especially on the morning peak in the circadian variation of ischemia could be that arousal of the sympathetic nervous system, with a consequent rise in blood pressure, heart rate, and myocardial oxygen demand, is a more important determinant of ischemia than coronary tonus, especially in the morning. In the evening, the sympathetic nervous system usually is less active, myocardial oxygen demand becomes a little lower, and drugs that improve myocardial oxygen supply, such as long-acting nitrates, may restore the oxygen supply-demand balance more easily. However, the fact that bisoprolol completely abolished the circadian variation of ischemia suggests that antagonism of sympathetic activity remains the most powerful tool to prevent or diminish ischemic events in the daily activities of our patients. In fact, bisoprolol improves the sympathico-vagal balance derived from the ratio of high- and low-frequency components of the heart rate variability.[19] Combination therapy added little to this already strong effect.

It was not possible to investigate to what extent nitrate tolerance accounted for the lower effectiveness of ISDN in our study, because the Holter monitoring and the ETT took place only at the end of each 4-week treatment period and the effect thus could not be compared with the beginning of treatment. In our dosage schedule of ISDN 20 mg TID, the last dose was taken at 6 PM in order to avoid nitrate tolerance, as has been shown in other studies.[12–14] The effectiveness of ISDN against anginal complaints and ST-depression during the ETT, and its relative effectiveness against ambulatory ischemia in the afternoon and evening hours, also argue against the occurrence of nitrate tolerance in our study.

The fact that exercise time was not significantly prolonged by either medication may be due to the selection of patients. Although all patients had anamnestic exercise-induced angina, they were selected on the basis of ST-depression during exercise and did not necessarily stop because of angina. In some patients exercise duration was already limited by fatigue or dyspnea on placebo. Active medication may also have caused early fatigue during exercise, an effect that is found more often in studies of beta-

adrenergic blockers. Whether this is true also for long-acting nitrates is not clear.

In studies of ischemic episodes recorded by Holter monitoring, the therapeutic effects may be overshadowed not only by day-to-day variability of the occurrence of ischemia, but also by a regression to the mean effect, if the presence of ischemic episodes is a selection criterion for entrance to the study.[20] In comparing the effect of two drugs in the same patients, regression to the mean may play a role in measuring the absolute effect, but not the relative effect of one drug compared with the other. To diminish the effect of day-to-day variability and thus diminish the regression to the mean, we used a relatively long, 48-hour, Holter measurement. According to a study by Deanfield and Spiegelhalter,[21] in a sample of 20 patients using 48-hour Holter monitoring, at least a 30% reduction in the number of ischemic episodes is required to have 80% power of reaching statistical significance. According to another study by Nademanee,[22] in a sample of 23 patients, with only 24-hour Holter monitoring, the reduction in duration of myocardial ischemia should be at least 47% to have 80% power of reaching statistical significance. In our study, with 23 patients and a 48-hour duration of the Holter monitoring, we may expect that $<30\%$ of the reduction in number of ischemic episodes and $<47\%$ of the reduction in duration of ischemia during the active treatments is due to regression to the mean. The reduction in number of ischemic episodes we found with ISDN was quite small, only 18%, which was not statistically significant, and argues against a substantial regression-to-the-mean effect. In contrast, the reduction in duration of ischemia with ISDN was much larger, 55%, which exceeded the estimated regression to the mean and was statistically significant. With bisoprolol or combination treatment, the reduction in all ischemic parameters in our study was far larger than the possible regression to the mean. But even if the effect of regression to the mean accounts for some of the decrease in ischemia during the active treatments, this decrease may be expected to be the same for all treatment phases. Thus the differences between bisoprolol or bisoprolol/ISDN treatment and ISDN treatment alone are certainly not influenced by this effect.

The therapeutic relevance of our findings is not yet clear. Whether effective treatment of all silent ischemia during daily activity leads to a better prognosis has not been prospectively proven. Ongoing long-term studies may answer this question.[23] The concordant positive influence of beta-adrenergic blockers on total ischemic burden, myocardial infarction, and sudden death suggests that there may be a positive influence of treatment.[24–26] The Atenolol Silent Ischemia Study suggests a positive influence of atenolol treatment on the occurrence of adverse events during 1-year follow-up of patients with silent ischemia, although the effect on mortality was not significant.[27] In contrast to beta- and adrenergic blockers

and calcium antagonists, no studies on the long-term cardioprotective effects of long-acting nitrates in silent ischemia have been performed. Future studies will have to determine whether the relative lack of influence of nitrates on ambulatory ischemia and its circadian variation is accompanied by a lack of long-term cardioprotection.

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